Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

August 25, 1999

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Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm 1061
Rockville, MD 20852

RE: Docket No. 99D-0529: Draft Guidance for Industry on Changes to an Approved NDA or ANDA: Notice of Availability and Request for Comments (64FR34660)

Dear Sir/Madam:

This letter is in reference to the FDA's notice of the "Draft Guidance for Industry on Changes to an Approved NDA or ANDA" published in the *Federal Register*, **64**, 34660 (June 28, 1999).

The US Food and Drug Administration's (The Agency) proposal to collapse separate sets of regulations for drug substances and drug products into a common guidance set based upon the scientific impact of the respective change(s) is reasonable and laudable. However, we have a number of broad concerns regarding the subject Guidance document, namely;

- **SUPAC** - This approach is risky in that a number of relevant SUPAC guidance documents that support this approach are not yet implemented (i.e. BACPAC-II, Stability Guidance, etc). To ensure that the efforts gained by SUPAC are not diminished, recommend that the timeframe between the final guidance and the issuance and/or revision of associated SUPAC's be kept short to minimize confusion during the implementation period;
- **Regulatory Burden** - The subject draft document seeks to extend the authority of the FDA in a number of areas (i.e. compliance with United States Pharmacopoeia [USP] monographs, etc) and increase the regulatory burden on the pharmaceutical industry which seems at odds with the intent of the November 21, 1997 Food and Drug Administration Modernization Act (FDAMA);

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- **Terminology (*Clarity*)** – The use of vague or broad terms or phrases (i.e. may, "any change", etc) should be avoided whenever possible. These "catch-all" terms and phrases do not add to the clarity of the expectations when, in accordance with the "validating the effects of the change" concept, the focus should be on the significance of the change. Recommend that the term "significant change" be used and defined as a change that is "likely to adversely affect the identity, strength, quality, purity or potency of the product . . . ";
- **Terminology (*Definition*)** - The addition of yet another definition of the term "validate" can only contribute to confusion in this area, especially in regarding to ICH global harmonization activities involving mutual recognition as well as the ICH-M4 (Common Technical Document) activities. Much more could be done in the definition section as well as the direct substitution of more appropriate term(s) (i.e. assessment, evaluate, etc) throughout the subject document than is currently done.

We appreciate the opportunity to comment on the subject draft guidance document and our specific comments/concerns regarding the various sections are provided below.

Sincerely,

Richard B. Phillips, Ph.D.
Director, Worldwide Regulatory Affairs (CM&C)

IV. Assessing the Effect of Manufacturing Changes

105 Per the Agency's Good Guidance Practices (GGP), further clarification should be provided with respect to the term "validated". Instead of the extensive reiteration of statutes and regulations at the beginning of this section, additional clarification of the boundaries expected of the assessment (i.e. single vs multiple batches; pilot vs full scale, etc) should be provided. Elevation of the associated footnote to the actual text would be a good example of the actual text.

106-114 There is a general concern that the intent of Sec 506A [356a] (a)(b) of The Act in its association of "validat[ion] of the change on the . . . product" with the distribution of the product falls under general cGMPs. In this context, it should remain the responsibility of the FDA field office to ensure "validation" and release of product for distribution. Further clarification should be made with respect to additional "validation of the effects" information (i.e. scale, number of batches, etc) required for "assessment" of the change.

IV. 2 Additional Testing

134-141 Often times the level of testing of commercial product differs from that applied during development. It would seem appropriate to have some indication that the "additional" testing referred to in this section is actually linked to that used during developmental studies as opposed to completely new tests.

> Example: Hardness and friability may not be a routine test for marketed product stability if initial development studies showed them to not represent a quality concern for the commercial dosage formulation. In order to assess the effect of a compositional change to the formulation, it would be a good idea to re-assess these parameters to confirm the original findings.

A provision should be included that would allow for information obtained during the initial developmental work (Pharmaceutical Development Report) to be used to justify a change. Since the effect of the change has already been studied during development, its effect on the product has already been "validated".

VI Sites

267-269 VI.B.4 While some of the subject information is harmonized with respect to issued SUPAC guidance documents (i.e. MR solid oral dosage forms) others are not (i.e. nasal spray pumps) as the *draft* guidance documents are not yet available.

271-273 VI.B.5 In order to be consistent within this sub-section, recommend including the following for clarity: " ... to a newly constructed, refurbished, or different *(not-previously cGMP approved)* aseptic processing facility". The second part of this sub-section allows for product site changes to the [*approved*] facility of products of similar types/process as a CBE supplement.

277-279 VI B.6. This section should exempt all solid dosage forms, not just modified release solid dosage forms from prior approval supplement.

Within the "validation of the effects of the change" concept, the primary packaging site of the final dosage form even where the primary package plays a role in actual drug delivery, should not impact the quality of the product if this is the only change. If there are no other changes in the drug product or container/closure system, then cGMPs should be the fundamental issue here.

311-313 IV.D. It is unclear which definition of "validated" is intended to apply with respect to the proposed Annual Report requirements in §314.70 (d)(3)(i) for what appears to be strictly cGMP related issues.

324-326 IV.D.5. Conflicts with section IV.D.7 below. This section exempts site changes within a single facility (except for sterile drug products) being reported to the Agency while section IV.D.7 requires a change in the floor plan (including "build-out[s]") be reported to the Agency.

333-334 IV D. 7. This section should be removed. General site floor plans are not part of the general filing requirement to NDAs or ANDAs and Type I DMFs for US based manufacturing sites have been eliminated. It is reasonable to expect the company to work with the FDA field office on such site "build-outs".

VII Manufacturing Process

344-360 VII.B.4. Recommend a general cross-reference to applicable SUPAC guidance document(s), which would include specific information for the stated examples.

VIII. Specifications

567-571 VIII. D.1. The proposed requirement constitutes an extension of the authority of the FDA with regard to the official compendia of the United States (i.e. USP), which is recognized in Section 501 of The Act as representing the official specification requirements for pharmaceuticals. The additional requirement that the specification for a listed drug "... is consistent with FDA requirements and provides *increased* assurance that the drug will have the characteristics ... that it is purported to have" is excessive.

IX. Package

588-606 IX.A The recently issued Container and Closure guidance document (June '99), references a pending guidance document regarding post approval changes not covered in the guidance. The specific examples given in this section regarding post-approval changes to packaging need to be harmonized with the pending guidance document.

666-667 IX.D. 3. How will CDER notify the industry regarding lists of "approved" primary package materials, especially those approved in other companies applications?

711-713 IX.D. 7. This section is excessive as information regarding secondary packaging (i.e. stock thickness, etc) is not generally supplied in detail (unless part of product protection).

XI. Miscellaneous Changes

795-797 XI.C.3. Information on in-house reference standards are not generally submitted to the Agency. The expectation is that they are equivalent to the reference standard information submitted in the original application.

798-799 XI.C.3. Tightening the specifications for a reference standard, without addressing the variability of the comparative analytical method, will not increase the assurance of product purity or potency.

XII. Multiple changes

804-805 It is reasonable to apply the strictest filing requirement where multiple changes involve various degrees of significance (i.e. minor and moderate). As the guidance is silent on multiple changes of the same significance level (i.e. moderate or minor), the expectation is that multiple changes of the same significance level (i.e. moderate, minor, etc) can be reported (i.e. CBE, AR, etc) can be reported for that specific level.

Glossary of Terms

832-834 Editorial comment regards the consistent use of terminology between the various guidance documents:

> Example: Primary guidance document defines "in-process material" to include drug product and "intermediate" to be drug substance specific while the draft June 1998 Stability guidance document (line 1514) uses "intermediate" to also refer to drug product blends (i.e. in-process material).

PARKE-DAVIS

Pharmaceutical Research
Division of Warner-Lambert Company
2800 PLYMOUTH RD. · P.O. BOX 1047 · ANN ARBOR, MI 48106-1047
PHONE: (734) 622-7000

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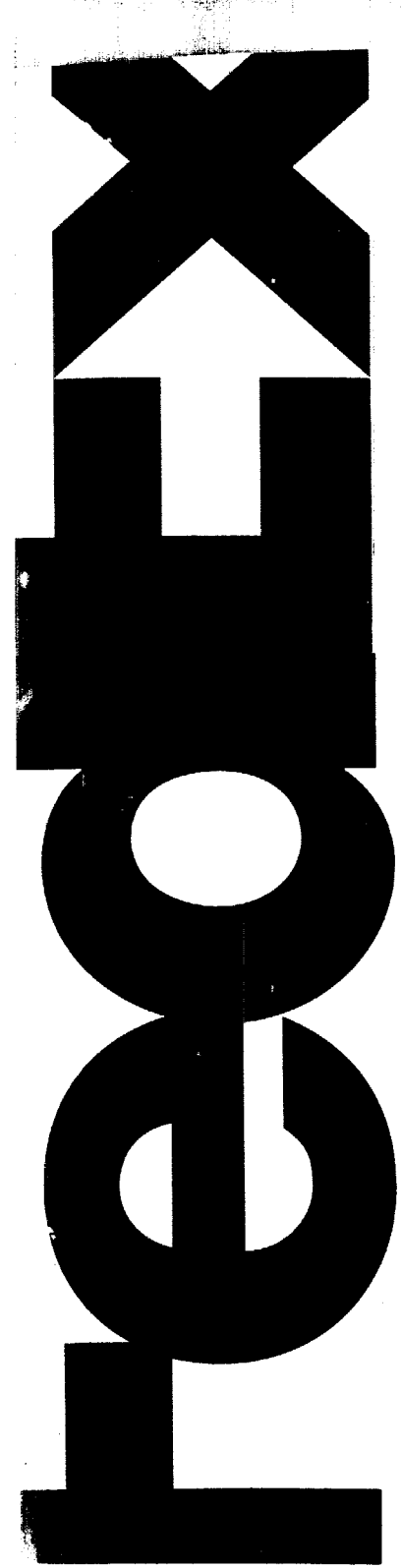

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PARKE-DAVIS
Pharmaceutical Research

Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

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Rockville, MD 20852